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Kidney, Urology and Hematology

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

KIDNEY, UROLOGY, AND HEMATOLOGY

Recent years have seen much progress in the fields of research supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases' (NIADDK) Division of Kidney, Urologic and Hematologic (KUH) Diseases. Some notable examples are:

- Kidney transplantation has become increasingly successful due to advances in surgical techniques and the use of new immunosuppressive drugs such as cyclosporine, antilymphocyte globulin, and antithymocyte globulin that help to prevent rejection of transplanted organs.
- Hemodialysis (use of an artificial kidney machine to remove poisonous wastes from the blood) and peritoneal dialysis (a procedure for filtering wastes using membranes in the abdomen) have been improved and ambulatory peritoneal dialysis has become a clinically effective alternative to other dialysis techniques in the treatment of end-stage renal disease in children.
- Research into the causes and mechanisms of kidney stone formation has brought about prevention of some kinds of stones as well as the more effective clinical management of already-formed stones than was possible just a few years ago.

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- Progress has been made in understanding the tissue changes and hormonal interactions involved in the epidemic disease benign prostatic hyperplasia (prostate enlargement), a serious health problem that affects most men over the age of 60.
- Scientists developed the "magnetic biopsy"--a magnetic noninvasive device that can be used outside of the body to determine the iron content of specific organs, allowing earlier identification of patients at risk of toxicity due to iron overload.
- Erythropoietin, a hormone regulating red blood cell production, has now been produced in vitro by molecular biologic techniques and can now be detected clinically by means of a new radioimmunoassay method that uses specific antibodies to the hormone. Tracing hormonal levels in patients and determining their precise actions should help scientists understand such diseases as aplastic anemia and polycythemia.

Despite these and other advances, a great deal of work remains to be done in the fields of kidney diseases, urology, and hematology. Kidney and urinary tract diseases affect over 13 million Americans and account for more than 80,000 deaths each year. The Federal Government spends almost $2 billion each year to provide maintenance dialysis and kidney transplantations for more than 87,000 patients with end-stage renal disease. It is anticipated that by 1990, more than 106,000 patients in this country will be kept alive with some form of chronic dialysis, at a projected annual cost exceeding $3.5 billion.

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Urinary tract infections are the second most common bacterial disease treated by physicians, and at least 8,000 patients die each year from infections of the kidney. More than a million Americans per year are hospitalized for the treatment of kidney and urinary tract stones. Approximately 270,000 prostatectomies are performed in the U.S. each year for the relief of urinary obstruction caused by the enlargement of the prostate gland, which occurs in many men over age 40 and most over the age of 60. The total cost of diagnostic procedures and treatment of this disorder alone exceeds $1 billion per year in the U.S.

The economic cost of blood diseases in the U.S. is in excess of $25 billion each year. The annual cost of lost productivity due to blood disorders is estimated to be nearly $3 billion, and deaths from these disorders total several hundred thousand annually.

This report describes selected highlights of the past year's progress in the fields of kidney disease, urology and hematology.

KIDNEY AND URINARY TRACT DISEASE RESEARCH

The goals of NIADDK's KUH division include prevention, early diagnosis, and treatment of kidney disease through development of an understanding of the basic mechanisms and causes of renal and urologic disorders. Areas of study include diseases such as glomerulonephritis, interstitial nephritis, kidney and bladder stones, polycystic kidney disease, diabetic nephropathy, analgesic-associated and other toxic nephropathies,

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immune disorders of the kidney, and benign prostatic hyperplasia. Prevention of chronic renal disease leading to end-stage kidney disease (ESRD) is an important target area. NIADDK-supported scientists are seeking ways to reduce the number of patients dependent on dialysis or renal transplantation to compensate for lost kidney function. Other goals include delineation of the basic causes of kidney stones, development of effective treatment for patients suffering with kidney stones, and the design of rational approaches to prevent the development of kidney stones.

Immunosuppressive Agents Prevent Kidney Failure in Lupus Nephritis

NIADDK intramural researchers recently reported results of long-term studies providing evidence that lupus nephritis patients treated with immunosuppressive drugs have a significantly reduced risk of developing progressive kidney disease which may lead to complete renal failure. They found that combining prednisone therapy with the immunosuppressive agents azathioprine or cyclophosphamide was superior to other combinations. These results agree with new evidence from grantees of NIADDK, who report results of a broad analysis of studies performed by many different investigators. Drs. David T. Felson and Jennifer Anderson of Boston City Hospital studied data pooled from previously published clinical trials in which patients were randomly assigned to receive either prednisone alone, or prednisone plus cyclophosphamide or azathioprine. The scientists found that in all of the studies, the combination

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therapy worked best. Rates of kidney damage, end-stage kidney disease, and death were all significantly lower in groups of patients receiving a cytotoxic agent combined with prednisone.

Role of Bacteria in the Formation of Renal Cysts

Adult polycystic disease of the kidney affects more than 200,000 Americans and is responsible for about 10 percent of patients receiving treatment for end-stage kidney disease. The cost to Medicare each year for treatment of polycystic kidney disease is approximately $180 million.

Institute grantee Dr. Kenneth Gardner, Jr., and his associates at the University of New Mexico, Albuquerque, have found that exposing germfree rats to a cyst-producing anti-oxidant chemical and then to contaminating organisms such as Staphyloccocus epidermidis, proteus, bacteroides and clostridia results in the formation of renal cysts. The researchers report that once the test animals were contaminated the disease process began almost immediately.

These findings strongly implicate infection-induced inflammation in the development of renal cysts and could lead to the scientific understanding of the causes of progression in polycystic kidney disease of man. Further studies are also needed to determine whether commonly occurring substances within the body such as superoxide dismutase, hydrocortisone and polymyoxin B are toxic to the kidneys and play a role in the progression of polycystic kidney disease.

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Multicenter Study of Nutritional Therapy in Progressive Kidney Disease

The Institute continues to support research on the influence of nutritional factors on the rate of progression of renal failure. Studies over the past several decades have indicated that dietary restriction of protein and/or phosphates may slow the rate of progression of several chronic renal disorders, retard kidney failure, and reduce the symptoms associated with renal diseases.

The Chronic Renal Disease/Renal Transplantation Program continues funding of a multicenter cooperative clinical study to test the hypotheses that: (1) restriction of dietary protein reduces the rate of progression of chronic kidney disease in humans; and (2) it is nutritionally safe to restrict dietary protein in patients with progressive kidney failure. The planning phase of the study has now been completed, and a pilot study involving 108 patients is under way. Eventually, more than 500 patients may participate in the full-scale study.

The investigators indicate that if the results of their studies prove that progression of the disease in a large proportion of patients can be arrested for many years, "the need for dialysis will be substantially reduced."

Progress in Understanding of Benign Prostatic Hyperplasia

New aspects of understanding and managing enlargement of the prostate gland were the focus of the Second NIADDK Symposium on the Study of Benign Prostatic Hyperplasia (BPH) that met this year. Dr. Gary Striker, director of the KUH division, called BPH

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an "epidemic disease" noting that more than half of men over the age of 50 suffer from BPH, and 95 percent of men in their seventies and eighties have the disorder.

NIADDK grantee Dr. Michael G. Mawhinney, professor of urology and pharmacology at the West Virginia University Medical Center, Morgantown, reported results of research on the role of stromal tissue in prostatic growth. Studies suggest that human BPH results from growth potential present in stromal tissue. Hormonal and biochemical interactions in such tissue have been found to correlate with abnormal prostatic growth in some instances. Dr. Mawhinney and other scientists in this field hope that their work will enable compounds to be produced that reduce the mass of prostate tissue, effecting a cure for BPH and providing an alternative to surgery.

Participants in the symposium expressed excitement over new areas of understanding that have been generated from studies of hormonal influences on prostate growth, from studies in neurology, and in the field of urodynamics. The scientists reported finding greater possibilities for comprehending the physical factors that produce BPH, for pursuing longitudinal studies, for using new urodynamic detection techniques, and for discovering drug techniques to manipulate growth of the prostate gland without adverse effects.

Preventive Immunization Against Urinary Tract Infection

Several investigators have reported immune responses in various species of animals following vaginal administration of antigens (substances that stimulate the immune system). Institute grantee Dr. David Uehling and his associates at the

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University of Wisconsin, Madison, are studying the effectiveness of the vaginal route of immunization in stimulating a local, protective immune response to bacterial antigens. These studies could provide the basis for developing the first effective vaccine against urinary tract infection (UTI) in women. UTI's afflict millions of women in the U.S. each year.

The researchers prepared a bacterial vaccine, which was subsequently instilled into the vaginas of test animals. The investigators demonstrated that when the vaginal route was used to immunize against E. coli bacteria, and the animals' bladders are subsequently infected by the same strain of bacteria, a rapid and strong immune response occurs in the bladders of the vaccinated animals that prevents infection. These data are of great importance since E. coli bacteria are the most common cause of urinary infection.

The scientists note that vaginal immunization can elicit an immune response in the entire lower urinary tract, including the bladder. Thus, it is possible to protect the bladder without risks and discomfort inherent in putting instruments into the bladder to directly induce the immune response. Studies so far have demonstrated that immunized animals show significantly fewer bacteria in the bladder than unimmunized animals as long as 21 days after infection. Further research is being conducted to determine the safety of the technique. Since there have been no alterations of the normal anatomy or physiology of the test animals in these studies, the investigators hope to extend their research to examining the immune responses of humans to the technique.

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HEMATOLOGY

The goal of research in hematology is to increase the fundamental and applied knowledge about blood and blood diseases. Major categories of this research effort are anemias of genetic origin, nutritional anemias, anemias associated with chronic diseases such as kidney failure and arthritis, disorders of blood cell production, metabolic disorders, and immunology. In addition, the availability of blood and blood cells facilitates study of membrane phenomena, protein structure and function, and other areas of research that provide information important to management of medical problems such as chronic renal insufficiency, transplantation, arthritis, nutritional disorders, and malignancy.

Blood diseases research is being spurred by remarkable advances in molecular genetics, which now hold hope for preventing or improving treatment of diseases of abnormal hemoglobin (the principal constituent of red blood cells) such as sickle cell disease and thalassemia through chemical modification of defective genes or blood proteins. New techniques also permit more precise study of specific genes that control formation of the protein component of hemoglobin.

Laser Technique Reveals Blood-Flow Patterns in Sickle Cell Patients

Dr. Griffin P. Rodgers of NIADDK's Laboratory of Chemical Biology and his colleagues at the National Institutes of Health have found a new, noninvasive method of monitoring the course and severity of sickle cell disease and of assessing the effects of treatment.

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Sickle cell anemia is a severe genetic disease in which red blood cells contain abnormal hemoglobin. These cells assume a sickle shape and are destroyed prematurely, leading to anemia. The cells can also block the flow of blood through capillaries, clogging the vessels and preventing blood from reaching tissues. The new technique, known as laser-Doppler velocimetry, can be applied painlessly to the forearms of patients. It bounces laser light off red blood cells in tiny blood vessels, enabling the researchers to compare patterns of blood flow.

The scientists have discovered that sickle cell patients show a unique pattern of blood flow, distinguishable from patterns in normal individuals or in patients with other types of anemia. The method could lead to new understanding and treatments of sickle cell disease and, possibly, of a variety of other disorders involving the heart and circulation.

Antithymocyte Globulin Treatment in Patients With Aplastic Anemia

Aplastic anemia is a progressive, usually fatal, disease characterized by bone marrow failure and consequent depression of the levels of all types of blood cells in the circulation, especially red blood cells. The treatment of choice is bone marrow transplantation if a matched sibling donor is available. Scientists are exploring ways to improve therapy for aplastic anemia patients.

When antibodies are produced against human lymphocytes (white blood cells) or thymocytes (cells of the thymus, an organ concerned with immune responses), the antibodies are found in

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the globulin fraction of blood serum. NIADDK grantee Dr. Lyle Sensenbrenner and his colleagues at the Johns Hopkins School of Medicine in Baltimore have found that injection of antibodies to lymphocytes into patients receiving bone marrow transplantation can result in suppression of cellular immune reactions against the transplanted tissue.

NIADDK scientists and other investigators have found that antithymocyte and antilymphocyte globulin therapies are effective in prolonging the lives of more than half of the aplastic anemia patients studied. The investigators ascribe the beneficial effects of these agents to their immunosuppressive activity. The precise mechanism of response of aplastic anemia patients to the globulins requires further study, however, as do questions concerning optimal administration of the agents, their effectiveness, and potential toxicity.

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